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Low-Dose Recombinant Human Growth Hormone Increases Body Weight and Lean Body Mass in Patients with Short Bowel Syndrome

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Objective

The authors investigate the effects of low dose recombinant human growth hormone (rhGH) on body composition and absorptive capacity in patients with short bowel syndrome from Crohn's disease.

Summary Background Data

Patients with short bowel syndrome usually are malnourished because of malabsorption. The anabolic effects of high doses of rhGH have been tested in different clinical catabolic conditions, recently including patients with short bowel syndrome. The authors have investigated the effects of low-dose rhGH in short bowel syndrome in a placebo-controlled crossover clinical trial.

Methods

Ten patients were treated with daily subcutaneous doses of rhGH/placebo (0.5 international units/kg^{-1} per $week^{-1}$ = 0.024 mg/kg^{-1} per day^{-1}) for 8 weeks in a randomized, double-blind, placebo-controlled crossover clinical trial with a minimum of 12 weeks wash-out. Absorptive capacity and biochemical parameters were investigated in a metabolic ward before treatment and during first and last week of treatment. Body composition was determined by DEXA-Scan (Lunar DPX, Scanexport Medical, Helsingborg, Sweden), impedance analysis, and whole body potassium counting.

Results

Low-dose rhGH doubled serum levels of insulin-like growth factor-1 (IGF-1) and increased body weight, lean body mass, and total body potassium by 5% ($p < 0.05$). Fat-free mass and total body water increased by 6% ($p = 0.008$). Increases in IGF-1 levels correlated with increases in fat-free mass ($r = 0.77$, $p < 0.02$). No significant changes in absorptive capacity of water, energy, or protein were detected.

Conclusion

Eight weeks of low-dose rhGH treatment leads to increases in body weight, lean body mass, and fat-free mass in patients with short bowel syndrome, correlated to increases in IGF-1 levels.

Patients with Crohn's disease have the risk of multiple intestinal resections because of recurrent inflammation or stenosis. In a small number of patients, this may lead to a short bowel syndrome. This syndrome is characterized by impaired net absorptive capacity of the remaining gut. Malabsorption of nutrients often necessitates nutritional support.

During the last few years, growth hormone has become more readily available because of recombinant DNA techniques; growth hormone has been used not only as replacement therapy, but also in many catabolic clinical conditions.[1] Recently, Byrne and coworkers[2,3] have reported beneficial acute effects of high-dose growth hormone in patients with massive intestinal failure. However, these studies were not placebo-controlled and the doses used were approximately 20 times higher than current growth hormone replacement doses.

We have conducted a randomized, double-blind, placebo-controlled crossover study to investigate the effects of low-dose recombinant human growth hormone (rhGH) on body weight, body composition, and absorptive capacity in patients with short bowel syndrome due to Crohn's disease.

PATIENTS AND METHODS

Patients

Clinical data of the patients are given in Table 1. Ten patients (3 women, 7 men; mean age 49 years; range, 30–72 years) with short bowel syndrome for more than 1 year because of Crohn's disease volunteered for the study. Clinical disease activity was absent or very low (Crohn's Disease Activity Index < 100). Mean body weight was 56 kg (range, 46–69 kg), mean body height was 1.74 m (range, 1.61–1.89 m) and body mass index was 18 kg/m^2 (range, 16–21 kg/m^2).

Two patients had slightly elevated serum aspartate aminotransferase activity and four had elevated alanine aminotransferase activity before the study. Alkaline phosphatase activity also was elevated slightly in three patients. Three patients had hemoglobin concentration below normal levels. All had normal fasting serum glucose concentrations. One patient lacked detectable amounts of α-tocopherol, and two patients had low absolute levels of α-tocopherol; however, this level became normal when corrected for low-serum cholesterol. All had serum total cholesterol values below 5 mmol/L. All patients exhibited normal 24-hour growth hormone profiles, with maximum peak values > 5 milliunits/L.

Mean remaining small intestinal length was 1.3 m (range, 0.9–1.7 m). Six patients had ileostomy/jejunostomy. Four patients had remaining large bowel.

Daily fecal/stomal outputs were 2.9 kg (range, 0.9–5.8 kg). All patients required oral or parenteral fluid substitution in combination with electrolytes, vitamins, and minerals. Eight patients also received food supplements. One patient required daily parenteral nutrition with 2700 kcal (11 MJ) through a central venous line. One patient had parenteral nutrition twice a week with 2000 kcal/week^{-1} (8.4 MJ), and one had intravenous infusions of physiological saline on demand, approximately once a month. One patient was reestablished on parenteral nutrition with 1900 kcal/day^{-1} (8 MJ) during the wash-out period before the second half of the study because of progressive malnutrition.

Study Design

Study design is outlined in Figure 1. The study was designed as a clinical prospective, randomized, placebo-controlled, double-blind investigation with low-dose rhGH/placebo during 8 weeks, separated by a wash-out period of at least 12 weeks. Criterium for eligibility was a stable short bowel syndrome, i.e, at least 10% below premorbid body weight with stable (±2 kg) weight and nutritional support during the last 6 months. Recombinant human growth hormone (Genotropin Kabi Pharmacia, Stockholm, Sweden) in a dose of 0.5 international units (0.17 mg)/kg^{-1} per week^{-1}, equivalent to 24 μg/kg^{-1} per day^{-1}, or 1.3 mg (4 international units) daily calculated from mean body weight, was administered subcutaneously each evening by the patients themselves. The vials contained 16 international units (5.3 mg) rhGH; the placebo vials contained the same vehicle and were indistinguishable visually. The randomization code was provided by the supplier and was broken after the last patient had completed the study. All patients gave informed consent after receiving written information on the protocol. The study was approved by the Ethical Committee of Sahl-

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Table 1. PATIENT DATA

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Body Mass Index (kg/m^2)	Large Bowel Function	Remaining Small Intestine (m)	Substitution*
1	M	47	58	176	18.7	Yes	1.0	Vitamin D, folic acid, multivitamins K, Mg, ORS food supplements
2	M	51	56	189	15.6	No	1.5	Multivitamins, ORS, Mg, Zn
3	M	29	57	176	18.4	Yes	1.15	Multivitamins, Mg (TPN in later part) food supplement
4	F	30	53	168	18.8	No	1.7	Vitamins, NaCl, Mg, K to TPN, ORS food supplement
5	F	50	54	164	20.1	No	1.0	Multivitamins Mg to PN, NaCl, food supplement
6	M	63	46	176	14.8	Yes	1.6	Mg, food supplement
7	M	40	62	175	20.2	Yes	0.9	Multivitamins, Mg, Ca, ORS, food supplement
8	M	71	55	170	19.0	Yes	1.0	Multivitamins, vitamin A + D, Fe, Mg, ORS
9	F	54	56	161	21.6	No	1.4	Multivitamins, Mg, NaCl, K, ORS, vitamin D, food supplement
10	M	49	70	185	20.4	No	1.3	Multivitamins, Mg, ORS, food supplement

ORS = oral rehydration solution.
* In addition to parenteral vitamin B12.

grenska University Hospital and by the Medical Product Agency of Sweden.

Methods

Body Composition Methods

Body weight was recorded each morning, in light clothing after voiding but before breakfast, on a Statmos scale to the nearest 0.1 kg. Body composition was determined during first or second day after admission. Lean tissue mass, body fat, bone mineral content, and bone mineral density were measured by dual-energy x-ray absorptiometry (DEXA-Scan, Lunar DPX, Scanexport Medical, Helsingborg, Sweden), and analyzed using software version 1.3. Coefficient of variation was 0.8%. The fat-free mass (FFM) by DEXA-Scan, *i.e.*, the sum of bone mineral content and lean tissue, is denoted as lean body mass (LBM).

Total body potassium (TBK) was determined by counting the 1.46 MEV radiation from the naturally present isotope potassium 40 (^{40}K) in a high sensitive 3 π-whole–body counter with a coefficient of variation of $\pm$2.2%.

Bioelectrical impedance analysis (BIA-101, RJL System. Inc., Detroit, MI) was used to estimate FFM, total body water, and body fat calculated as previously described.[4]

Metabolic Balance Methods

Metabolic balance investigations were performed for 4 days before, at the beginning, and at the end of each 8-

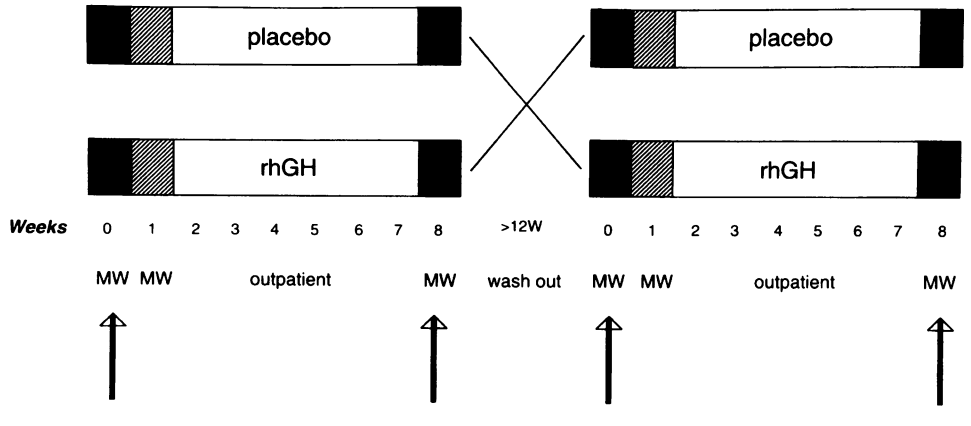

Figure 1. Study design. MW = metabolic ward balance study during 4 days; Arrow = determination of body composition and biochemical monitoring.

week treatment period. During these investigations, patients stayed at the metabolic ward, with individualized and controlled food from the metabolic ward kitchen and complete collection of urine and feces/stomal outputs. Fecal samples were collected and pooled in 4-day batches that were lyophilized and mixed meticulously before analysis. All food for each patient was prepared batchwise in advance and stored before use. Each patient had an individually composed low-fat, high-carbohydrate menu, with ordinary food items and additional food supplements according to habitual diet, during all metabolic investigations on each treatment period. During these metabolic balance periods, food intake was planned to be constant, and any leftovers were collected for subsequent analysis to have the food intake figures as exact as possible.

Energy content was determined by combustion in a bomb calorimeter (Gallenkamp, Loughborough, Leicestershire, UK); nitrogen in fecal samples and food duplicates was analyzed by a modified Kjeldahl technique,[5] and urinary nitrogen was determined by chemoluminescence (Antek Instruments, Houston, TX). Sodium and potassium levels were measured by flame photometry, and calcium and magnesium levels were measured by atomic absorptiometry. Duplicate portions of the diets were collected and analyzed in the same runs as the fecal samples. Absorptive capacity in percent was expressed as $(1 - (\text{excretion/intake})) \times 100$.

Biochemical Assays

Blood samples were taken in the morning, before breakfast. Patient sera were collected and stored at −20 C until analyzed in one batch for each of the following determinations: insulin-like growth factor-1 (IGF-1), IGF-1 binding protein 3, and intact parathyroid hormone; these were were determined by radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA). Osteocalcin was determined by a double-antibody radioimmunoassay (International CIS, Gif-sur-Yvette, France). Free triiodothyronine (T3) was determined by a ligand-analogue radioimmunoassay (Amerlex M, Kodak Clinical Diagnostics, Amersham International, Aylesbury, Buckinghamshire, UK).

Serum retinol and α-tocopherol were determined by high-pressure liquid chromatography.[6] Serum concentrations of magnesium and zinc were determined by atomic absorptiometry.

Twenty-four–hour growth hormone profiles were determined before the study. Growth hormone was determined by an radioimmunoassay (Pharmacia, Uppsala, Sweden) with a detection limit of 0.30 mU/L, as described previously.

Methods currently used at the Department of Clinical Chemistry at Sahlgrenska University Hospital were used during the study for the following levels: hemoglobin, glucose, serum electrolytes, creatinine, total protein, bilirubin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, aspartate aminotransferase (Enzyme Commission [EC] 2.6.1.1.), alanine aminotransferase (EC 2.6.1.2.), and alkaline phosphatases (EC 3.1.3.1.).

Statistics

The study was designed to detect changes in absorptive capacity of 2% to 3% and body composition of 5% during rhGH treatment, with a power of 90% at a significance level of 0.05. Accordingly, the study was not designed to detect *differences in changes* between rhGH and placebo as in classical placebo-controlled crossover studies, mainly because of the great intraindividual variation in patients with short bowel syndrome.

All values are given as mean ± standard error of the mean, unless otherwise stated. Treatment effects during growth hormone and placebo periods were evaluated with Wilcoxon's signed ranks test, with $p < 0.05$ considered to be statistically significant. Spearman's coefficient correlation was used. Time trends and period effects also were investigated by analysis of variance, using a computer package (SYSTAT 5.1, Systat Inc., Evanston, IL) for the calculations.

RESULTS

Compliance, Side Effects, and Subjective Experiences

All patients completed the study, although one reduced the prescribed dose to 20% because of nightmares, nasal obstruction, and an exanthema during the first week of treatment. Two patients noticed slight muscle stiffness during active treatment. Two patients had increased heart rate during the first week of rhGH treatment. Three patients noticed slight stiffness of joints, but no one developed clinical edema or arthralgia. Two patients had slightly swollen fingers during placebo treatment, but not on rhGH treatment. Transient gynecomastia developed in one patient during rhGH treatment, and one patient reported numbness in hands on active treatment. Five patients experienced less chilliness on rhGH therapy.

One patient had previously been treated with total parenteral nutrition years before the study. He gradually lost weight during the wash-out period and was reinstituted on parenteral nutrition for the second part of the investigation, which turned out to be the placebo period. One patient had an elective median nerve decompression performed during the rhGH period and hypokalemia with increased potassium substitution together with dixyrazine for anxiety during the placebo period. Another patient reduced the parenteral feeding during the placebo period

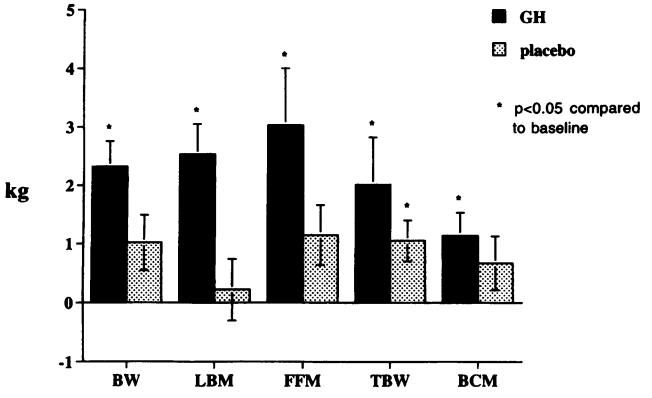

Figure 2. Changes in body composition during 8 weeks treatment with low-dose recombinant human growth hormone and placebo in ten patients with short-bowel syndrome. BW = body weight; LBM = lean body mass; FFM = fat-free mass; TBW = total body water; BCM = body cell mass.

because of nausea and recurrent abdominal pain requiring opioid analgetics.

Body Weight and Body Composition

Values on body weight and body composition are summarized in Figure 2 and Table 2. During the 8-week placebo period, there were no significant changes in body weight or body composition, except an increase in total body water of 1.0 ± 0.3 kg ($p = 0.008$).

During active treatment with rhGH, body weight increased by 2.3 ± 0.8 kg ($p = 0.005$). Lean body mass increased 5.6 ± 1.9% ($p = 0.005$), and body fat did not change significantly. Total body potassium increased by 137 ± 47 mmol ($p = 0.013$), equivalent to 1.1 ± 0.4 kg body cell mass. Fat-free mass increased 6.4 ± 2.0% ($p = 0.008$), as estimated by bioelectrical impedance analysis, with an increase of 5.5 ± 2.2% in total body water. There was a strong correlation between LBM, as estimated by DEXA-Scan, and FFM, as estimated by bioelectrical impedance analysis ($r = 0.95$, $p < 0.01$). Increases in FFM during rhGH treatment were positively and significantly ($r = 0.77$, $p < 0.02$) correlated to the relative increases in IGF-1. There also was a correlation between increases in body weight and IGF-1, but without statistical significance ($r = 0.48$).

Bone measurements by DEXA-Scan are summarized in Table 3. There were small but significant changes in bone mineral content, which increased by 21 g (1 ± 0.4%; $p = 0.028$) and in estimated total bone calcium, which also increased by 1 ± 0.4% (8 g; $p = 0.028$). No significant changes were seen in total body bone mineral den-

Table 2. MEASUREMENTS OF BODY WEIGHT, TOTAL BODY POTASSIUM, LEAN BODY MASS, BODY FAT, FAT FREE MASS, AND TOTAL BODY WATER IN TEN PATIENTS WITH SHORT BOWEL SYNDROME TREATED WITH RECOMBINANT HUMAN GROWTH HORMONE AND PLACEBO FOR 8 WEEKS EACH

Variable	Baseline	8 weeks	Change (%)
Weight (kg)			
rhGH	57.3 ± 2.3	59.6 ± 2.4*	+4.0
Placebo	57.0 ± 2.0	58.0 ± 2.1	+1.8
Total body potassium (mmol)			
rhGH	2898 ± 181	3035 ± 165*	+4.7
Placebo	2890 ± 178	2970 ± 181	+2.8
DEXA measurements			
Lean body mass (kg)			
rhGH	46.8 ± 2.5	49.3 ± 2.6*	+5.6
Placebo	47.5 ± 2.7	47.5 ± 2.4	0
Body fat (kg)			
rhGH	9.9 ± 1.9	9.8 ± 2.0	−1.0
Placebo	9.6 ± 1.9	10.0 ± 1.8	+4.2
BIA measurements			
Fat free mass (kg)			
rhGH	47.9 ± 2.3	50.9 ± 3.0*	+6.3
Placebo	47.3 ± 2.4	48.4 ± 2.3	+2.3
Total body water (kg)			
rhGH	38.2 ± 2.2	40.1 ± 2.6*	+5.0
Placebo	36.4 ± 2.0	37.4 ± 2.9*	+2.7

rhGH = recombinant human growth hormone; DEXA = scan, Lunar DPX, Scanexport Medical, Helsingborg, Sweden; BIA = bioelectrical impedance analysis.
* Significant changes *vs.* baseline ($p < 0.05$) evaluated by Wilcoxon's signed rank test.
Values are mean ± standard error of the mean.

Table 3. MEASUREMENTS OF BONE MINERAL DENSITY AND BONE MINERAL CONTENT IN TEN SHORT BOWEL PATIENTS TREATED WITH RECOMBINANT HUMAN GROWTH HORMONE AND PLACEBO FOR 8 WEEKS EACH

Variable	Baseline	8 weeks	Change (%)
Total body bone mineral density (g/cm^2)			
rhGH	0.997 ± 0.03	1.001 ± 0.03	+0.4
Placebo	0.997 ± 0.04	0.999 ± 0.03	+0.2
Bone mineral content (g/cm^2)			
rhGH	2184 ± 121	2205 ± 122*	+1.0
Placebo	2181 ± 136	2190 ± 135	+0.4
Total bone calcium (g)			
rhGH	830 ± 46	838 ± 46*	+1.0
Placebo	829 ± 52	832 ± 51	+0.4
Lumbar bone mineral density (g/cm^2)			
rhGH	0.96 ± 0.05	0.96 ± 0.05	0
Placebo	0.95 ± 0.06	0.95 ± 0.05	0
Femural neck bone mineral density (g/cm^2)			
rhGH	0.713 ± 0.04	0.736 ± 0.04	+3.2
Placebo	0.734 ± 0.04	0.709 ± 0.03	−3.4

rhGH = recombinant human growth hormone.
*$p < 0.05$ *vs.* baseline evaluated by Wilcoxon's signed rank test.

sity. There were no statistically significant carry-over effects on body composition over the wash-out period of a minimum of 12 weeks.

Metabolic Balance Study

During the 4 days of metabolic balance investigations, body weight increased by a mean of 1.0 ± 0.3 kg (range, 0.3–2.6 kg; $p < 0.04$). This was the case during baseline investigation before treatment, as well as during first week of rhGH and placebo periods, and during the last treatment week.

Mean daily energy intake from food was 3500 kcal (14.6 MJ; range, 1900–6000 kcal, 7.9–25 MJ), corresponding to 63 kcal (0.26 MJ)/kg^{-1} per day^{-1} (range, 38–103 kcal [0.15–0.42 MJ]/kg^{-1} per day^{-1}). On average, protein intake was 176 g/day (range, 125–287 g/day). Fat intake was on average 103 ± 4 g/day, corresponding to 24 ± 0.4% of the total food energy coming from fat. Dietary fiber intake was 31 ± 4 g/day (range, 16–54 g/day). Sodium intake was 431 ± 62 mmol/day, potassium intake was 203 ± 14 mmol/day, calcium intake was 82 ± 12 mmol/day, and magnesium intake (mostly from supplements) on average 72 ± 5 mmol/day. Urinary nitrogen excretion was 11.9 ± 1.6 g/day^{-1} before and 11.6 ± 1.2 g/day^{-1} after rhGH treatment, whereas nitrogen excretion before and after placebo was 11.2 ± 1.8 g/day^{-1} and 12.0 ± 1.8 g/day^{-1} respectively, indicating a protein turnover of 1.3 g/kg^{-1} per day^{-1} (range, 0.9–2.2 g/kg^{-1} per day^{-1}).

Absorptive capacity during metabolic investigation before treatment was 44 ± 9% for fluid, whereas apparent absorption of energy was 60 ± 6% and nitrogen was 55 ± 6%. After rhGH treatment, these figures basically were unchanged, 45 ± 10%, 61 ± 6%, and 54 ± 6%, respectively. Absorptive capacity before and after placebo treatment was 36 ± 12% and 43 ± 10% for fluid, 57 ± 6% and 58 ± 6% for energy and 50 ± 6% and 51 ± 6% for nitrogen. Absorptive capacity before treatment was as follows: for sodium, 43 ± 15%; for potassium, 62 ± 8%; for calcium, 8± 4%; and for magnesium, 8 ± 5%. After rhGH treatment, these figures were 46 ± 18%, 65 ± 8%, 6 ± 3%, and 7 ± 4%, respectively. After placebo treatment, the absorptive capacity was 47 ± 16% for sodium, 60 ± 8% for potassium, 11 ± 2.4% for calcium, and 2 ± 4% for magnesium. No aspects of absorptive capacity were different during placebo and rhGH treatment when tested individually by Wilcoxon's signed ranks test.

There were no significant changes in urinary excretion of nitrogen, electrolytes, and minerals, nor in the metabolic nutrient balances during placebo or rhGH treatment. There was a nominal reduction of 5.4% (162 g) of fecal/stomal output after rhGH treatment (not significant). There also was an improved nitrogen balance during the first treatment week, with 4.8 ± 2.9 compared to 2.3 ± 2.9 g/day^{-1} ($p = 0.011$) on rhGH and placebo, respectively.

Biochemical Assays

During placebo treatment, there were no significant changes in any of the serum variables measured.

During rhGH treatment, serum concentration of IGF-1 increased 91% from 207 ± 32 μg/L before treatment to 396 ± 65 μg/L ($p = 0.005$). Insulin-like growth factor-1 binding protein 3 increased 35% from 2.36 ± 0.3 mg/L to 3.15 ± 0.3 mg/L ($p = 0.005$).There was a small but significant decrease in serum sodium concentration during rhGH treatment, from 137 ± 0.8 mmol/L to 136 ± 0.8mmol/L. Osteocalcin increased from 13 ± 1.9 to 15.8 ± 1.9 μg/L (21%; $p = 0.047$) during rhGH treatment. Patients with elevated transaminase activity responded in the same way as patients with normal activity. Serum values for other minerals and electrolytes such as potassium, calcium, magnesium, and zinc were unchanged during rhGH treatment. Serum proteins such as albumin, prealbumin, transferrin, gastrin, ferritin, retinol-binding protein, and alkaline phosphatase also were unchanged after rhGH treatment. Hormone levels of insulin, triiodothyronine, parathyroid hormone, as well as vitamins such as retinol and tocopherol, also were unchanged during treatment. Blood hemoglobin and glucose concentrations were not affected by rhGH treatment.

DISCUSSION

To the best of our knowledge, this is the first double-blind placebo-controlled, crossover study on the effects of growth hormone in patients with short bowel syndrome.

The results show that 8 weeks of treatment increased body weight and DEXA-Scan–measured LBM by 5% without affecting fasting blood glucose or insulin levels. Fat-free mass and total body water estimated by bioelectrical impedance analysis increased by approximately 6%. Mean serum levels of IGF-1 are seen to double, but with great interindividual variation. The increase in IGF-1 was correlated to the increase in FFM and also, but not statistically significant, to the increases in LBM and body weight. No changes were seen in the intestinal absorptive capacity or in the metabolic balances.

This investigation is presented on an intent-to-treat basis, despite the fact that some of the patients had different medical or nutritional treatments during the study. Taken together, these modifications tend to reduce the power to detect any differences between placebo and treatment with rhGH. Patients with short bowel syndrome seldom are clinically stable for a long period of time.[7] They often are underweight, trying to cope with massive enteral losses by the intake of large amounts of food, fluids, nutritional supplements, and enteral or parenteral feedings.[8,9] This certainly was true of the patients in the present investigation.

When confined to the metabolic ward, energy intake by mouth was 41 kcal/kg per day, which should be sufficient to maintain body weight. Nutritional requirements for protein also should be met with a protein turnover of 1.2 g/kg per day, calculated from urinary nitrogen excretion. In fact, this produced a significant increase in body weight during the days spent in the metabolic ward. Similar effects were not attained outside the metabolic ward, except when rhGH was administered.

We found no sustained effect of rhGH on body composition over the wash-out period, which was at least 12 weeks; however, in some cases, this period continued for more than 24 weeks, for logistic reasons. There is one report on sustained body weight for several months after rhGH treatment in short bowel syndrome, but these improvements were uncontrolled, and the mean body weight actually decreased compared with baseline 1 year after treatment.[3] According to the results of the present study, it probably is necessary to continue low-dose rhGH treatment for a longer period of time for the anabolic effects of rhGH to be sustained. Specific dietary measures might offer other solutions, as have been suggested by the studies of Byrne and coworkers.[3]

Adequate nutrition is important for attaining normal values of IGF-1, and patients with short bowel syndrome might be expected to have depressed IGF-1 levels. In the present study, the basal levels of IGF-1 were within the normal range but were nonetheless doubled by low-dose rhGH treatment. However, the determination of IGF-1 was performed on blood samples taken in the morning after at least 4 days of optimal nutritional therapy. The IGF-1 levels conceivably might have been lower if they had been determined on admission to the metabolic ward. This is supported by the observation that in eight of the patients in the study for whom IGF-1 previously had been determined before admission, the levels were lower than after 4 days at the metabolic ward (165 ± 26 μg/L *vs.* 205 ± 34 μg/L; $p < 0.05$).

Several short-term studies have confirmed the potential anabolic effects of high-dose growth hormone in catabolic conditions[10,11] and as adjuvant to parenteral nutrition.[12] There is much less information on medium-[13] or long-term investigations or with low-dose growth hormone.[14,15] Furthermore, only two reports from the same group of investigators has focused on patients with short bowel syndrome.[2,3]

In a parallel design using high doses of growth hormone (approximately 6 times the doses given in the present investigation) together with aggressive nutritional support during a short period of time, Byrne and coworkers[2] recently reported similar results in 10 of 18 patients studied. Recently, nutrient absorption has been reported to increase in patients with severe short bowel syndrome when high doses of growth hormone together with glutamine and soluble fiber were given for 3 weeks on a metabolic ward.[3] However, that investigation was an open, uncontrolled study. In the present double-blind, placebo-controlled, crossover study, there were no significant dif-

ferences in absorptive capacity after 8 weeks of treatment with low-dose rhGH. However, there was an increase in LBM and in TBK, which could be due to better absorption or an improved use of absorbed nutrients. There was a small nominal improvement in potassium absorption from 61% to 65%, but this was not statistically significance and there was no detectable change in urinary potassium excretion. Mean increase in TBK during growth hormone treatment was 137 ± 47 mmol, which could be attained by increased absorption of no more than 2.5 ± 0.8 mmol potassium per day, which corresponds to an increased absorptive capacity of potassium that would be difficult to detect by short-term metabolic balance investigations, given the great variation in absorptive capacity in these patients. The increases in body weight, LBM, and body cell mass during rhGH therapy, as found in this study without significant improvements in the absorptive capacity, indicate an enhanced efficiency in the use of nutrients in agreement with earlier studies on the effects of growth hormone in man,[16] and also are consistent with the results of Byrne and coworkers.[2]

The broad range of IGF-1 responses to rhGH treatment was correlated to the increases in FFM and nominally to the increases in LBM. The alteration of IGF-1 levels on active treatment suggests that the dose of rhGH should be monitored and adjusted subsequently, in accordance with the current strategy for growth hormone substitution therapy. In fact, IGF-1 levels have been reported earlier to correlate with improvement in nitrogen balance.[17]

Serum levels of osteocalcin increased by 21% during rhGH treatment, indicating increased bone formation. This is in accordance with what has been found previously during longer treatment periods in growth-hormone deficient patients on replacement therapy with rhGH.[18,19] Bone mineral content increased slightly, as estimated by DEXA-Scan. It currently is not known whether prolonged therapy with low-dose rhGH could increase bone mineral density in patients with short bowel syndrome, similar to the findings in patients who are growth-hormone deficient.[19] It would be of clinical significance because the patients in the present study had total bone densities at only 89 ± 3% of age- and sex-matched controls, and eight out of ten patients were considered osteoporotic, as estimated by DEXA-Scan. This could be explained by low body weight and malabsorption of calcium and fat soluble vitamins accompanying steatorrhea.

Total body potassium is known to correlate well with body cell mass and total muscle mass, both of which are strong determinants of physical working capacity.[9] The increase in TBK was parallel to the increase in LBM because the quotient TBK/LBM did not change significantly during treatment. This implies that the increases in FFM and LBM were derived both from increased body cell mass and extracellular water. Thus, an increase in TBK of 5%, as found in this investigation, presumably also would increase the working capacity in patients with short bowel syndrome.

The increase in TBK also may reflect repletion of body potassium stores, increasing the intracellular concentration of potassium , although this seems unlikely because the urinary potassium excretion did not change during treatment. The increase in TBK also may reflect potassium accumulated within glycogen stores, in itself a favorable improvement in these undernourished patients which cannot be ruled out from these measurements. However, TBK and LBM increased in parallel, and subsequently, the ratio LBM to TBK did not change. Total body water increased similarly, indicating a parallel increase in intra- and extracellular water. Further investigations are needed to discover if rhGH treatment improves the formation of muscle mass and physical function in these patients.

This study demonstrates that low-dose rhGH treatment during 8 weeks increases body weight, LBM, total body water, bone mineral content, and body cell mass, as estimated from TBK without clinical edema or signs of altered glucose metabolism. Thus, low-dose rhGH treatment could be acceptable as a complement to intensive conventional nutrition support for patients with short bowel syndrome, if used under close medical and metabolic supervision, and currently only within controlled clinical trials. It remains to be investigated whether these beneficial effects would progress during a longer treatment period and whether the increments in LBM improve functional capacity.

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